

APPENDIX "A"

Examples of drugs and non-peptides which have been discovered by ligand-based receptor screens.

	Drug/non-peptide	Radiolabel For Screening	Reference	Targeted Receptor
5	Zantac	[³ H]-Histamine	1	Histamine H2
	Tagamet	[³ H]-Histamine	1	Histamine H2
	Seldane	[³ H]-Histamine	1	Histamine H1
	Ventolin	[³ H]-Noradrenaline	2	Adrenergic β 2
	Atenolol/Tenermin	[³ H]-Adrenaline	2	Adrenergic β 1
10	Propanolol/Inderal	[³ H]-Noradrenaline	2	Adrenergic β 1/ β 2
	Prazosin	[³ H]-Adrenaline	3	Adrenergic α 2B/2C
	Isoproterenol/Isordil	[³ H]-Noradrenaline	2	Adrenergic β 1/ β 2
	Norepinephrine/Levophed	[³ H]-Adrenaline	2	Adrenergic α 1/2, β 1/2/3
15	Imitrex	[³ H]-5HT	4	Serotonin 5HT-1D
	Buspar	[³ H]-5-HT	4	Serotonin 5HT-1A
	Nefazodone	[³ H]-Ketanserin	5	Serotonin 5HT-2A
	Thorazine	[³ H]-Dopamine	6	Dopamine D2
	Clozapine	[³ H]-Dopamine	9	Dopamine D2
20	Codeine	[³ H]- β endorphin	7	Opioid Receptors
	Morphine	[³ H]- β endorphin	7	Opioid Receptors
	Methadone	[³ H]- β endorphin	7	Opioid Receptors
	RO-46-2005 PD 156707 SB 209670	[¹²⁵ I]-Endothelin	8	Endothelin
25	MK-954	[¹²⁵ I]-Angiotensin II	9	Angiotensin II
	CP-154,526	[¹²⁵ I]-CRF	10	CRF
	BIBP 3226	[¹²⁵ I]-NPY	11	NPY
	SR-48968	[¹²⁵ I]-Neurokinin	12	Neurokinin

SR-49059	[¹²⁵ I]-Vasopressin	13	Vasopressin
L-366,509	[¹²⁵ I]-Oxytocin	14	Oxytocin
NK-1/NK-2	[¹²⁵ I]-Tackykinin	15	Tackykinin
LY303870	[¹²⁵ I]-Substance P	16	Substance P
5 HS-142-1	[¹²⁵ I]-ANP	17	ANP
L-365,269-CR 1505	[¹²⁵ I]-CCK	18	CCK
SR 48527	[¹²⁵ I]-Neurotensin	19	Neurotensin
WIN 64338	[¹²⁵ I]-Bradykinin	20	Bradykinin

References

- 10 1. Hill, S. (1990). Distribution properties and functional characteristics of three classes of histamine receptor. *Pharmacol. Review.* 7, 1-51.
2. Bylund, D. (1994). International union of pharmacology nomenclature of adrenoceptors. *Pharmacol. Review.*, 46, 121-136.
- 15 3. Hieble, J. (1995). International union of pharmacology. X. Recommendation for nomenclature of α 1-adrenoceptors. *Pharmacol. Review.*, 47, 267-270.
4. Peroutka, S. (1995). Serotonin receptor subtypes. Their evolution and clinical relevance. *CNS Drugs.* 4, 19-28.
5. Baxter, G. (1995). 5-HT₂ receptors: a family re-united? *Trends Pharmacol. Sci.* 16, 105-110.
- 20 6. Seeman, P. & Van Tol, H. (1994). Dopamine receptor pharmacology. *Trends Pharmacol. Sci.* 15, 264-270.
7. Knapp, R. (1995). Molecular biology and pharmacology of cloned opioid receptors. *FASEB J.* 9, 516-525.
- 25 8. Reynolds, E.E. (1995). Pharmacological characterization of PD 156707, an orally active ETA receptor antagonist. *J. Pharmacol. Exp. Ther.*, 273:3, 1410-7. Gellai, M. et al (1995). Nonpeptide endothelin receptor antagonists. V: Prevention and reversal of acute renal failure in the rat by SB 209670. *J. Pharmacol. Exp. Ther.*, 275:1, 200-6. Clozel, M. et al (1993). In vivo pharmacology of Ro 46-2005, the first synthetic nonpeptide endothelin receptor antagonist: implications for endothelin physiology. *J. Cardiovasc. Pharmacol.*, 22 Suppl 8:, S377-9.
- 30 9. Chen, T.S. et al (1993). Microbial hydroxylation and glucuronidation of the angiotensin II (AII) receptor antagonist MK 954. *J. Antibiot. (Tokyo)*, 46:1, 131-4. Palkowitz, A.D. et al (1994). Structural evolution and pharmacology of a novel series of triacid angiotensin II receptor antagonists. *J. Med. Chem.*, 37:26, 4508-21.

10. Martone, R.L. et al (1996). Human CRF receptor chimeras: mapping of ligand binding determinants. Abstract 609.8. 26th meeting for the society of neuroscience, Washington, D.C., November 16-21, 1996.
- 5 11. Sautel, M. et al (1996). Neuropeptide Y and the nonpeptide antagonist BIBP 3226 share an overlapping binding site at the human Y1 receptor. *Mol. Pharmacol.*, 50:2, 285-92.
12. Advenier, C. et al (1992). Effects on the isolated human bronchus of SR 48968, a potent and selective nonpeptide antagonist of the neurokinin A (NK2) receptors. *Am. Rev. Respir. Dis.*, 146:5 Pt 1, 1177-81.
- 10 13. Serradeil-Le Gal, C., et al (1993). Biochemical and pharmacological properties of SR 49059, a new, potent, nonpeptide antagonist of rat and human vasopressin V1a receptors. *J. Clin. Invest.*, 92:1, 224-31.
14. Pettibone, D.J. & Clineschmidt, B.V. (1993). Development and pharmacological assessment of novel peptide and nonpeptide oxytocin antagonists. *Regul Pept*, 29, 45:1-2. Evans, B.E. et al (1992). Orally active, nonpeptide oxytocin antagonists. *J. Med. Chem.*, 35:21, 3919-27.
- 15 15. Kudlacz, E.M. et al (1996). In vitro and in vivo characterization of MDL 105,212A, a nonpeptide NK-1/NK-2 tachykinin receptor antagonist. *J. Pharmacol. Exp. Ther.*, 277:2, 840-51.
- 20 16. Gitter, B.D. et al (1995). Pharmacological characterization of LY303870: a novel, potent and selective nonpeptide substance P (neurokinin-1) receptor antagonist. *J. Pharmacol. Exp. Ther.*, 275:2, 737-44.
- 25 17. Imura, R. et al (1992). Inhibition by HS-142-1, a novel nonpeptide atrial natriuretic peptide antagonist of microbial origin, of atrial natriuretic peptide-induced relaxation of isolated rabbit aorta through the blockade of guanylyl cyclase-linked receptors. *Mol. Pharmacol.*, 42:6, 982-90. Oda, S. et al (1992). Pharmacological profile of HS-142-1, a novel nonpeptide atrial natriuretic peptide (ANP) antagonist of microbial origin. II. Restoration by HS-142-1 of ANP-induced inhibition of aldosterone production in adrenal glomerulosa cells. *J. Pharmacol. Exp. Ther.*, 263:1, 241-5.
- 30 18. Pendley, C.E. et al (1993). The gastrin/cholecystokinin-B receptor antagonist L-365,260 reduces basal acid secretion and prevents gastrointestinal damage induced by aspirin, ethanol and cysteamine in the rat. *J Pharmacol Exp Ther*, 265:3, 1348-54. Rakovska, A. et al (1993). Effect of loxiglumide (CR 1505) on CCK-induced contractions and 3H-acetylcholine release from guinea-pig gallbladder. *Neuropeptides*, 25:5, 271-6. De Dios, I. & Manso, M.A. (1994). Effect of L-364,718 (CCK receptor antagonist) on exocrine pancreatic secretion of hydrocortisone-treated rats. *Pancreas*, 9:2, 212-8.
- 35 19. Labbe-Jullie, C. (1994). Effect of the nonpeptide neurotensin antagonist, SR 48692, and two enantiomeric analogs, SR 48527 and SR 49711, on neurotensin binding and contractile responses in guinea pig ileum and colon. *J. Pharmacol. Exp. Ther.*, 271:1, 267-76.
- 40

20. Sawutz, D.G. et al (1995). Pharmacology and structure--activity relationships of the nonpeptide bradykinin receptor antagonist WIN 64338. *Can. J. Physiol. Pharmacol.*, 73:7, 805-11.